CAROTID INTIMA MEDIA THICKNESS AS A MARKER OF CORONARY ARTERY DISEASE IN TYPE 2 DIABETES MELLITUS

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CERTIFICATE

This is to certify that this dissertation titled **"CAROTID INTIMA MEDIA THICKNESS AS A MARKER OF CORONARY ARTERY DISEASE IN TYPE 2 DIABETES MELLITUS"** submitted by **Dr. M. SAMPATH KUMAR** to the faculty of General Medicine, The Tamilnadu Dr. M.G.R. Medical University, and Chennai in partial fulfillment of the requirement for the award of MD degree Branch I (General Medicine) is a bonafide research work carried out by him under our direct supervision and guidance.

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I, Dr. M. SAMPATH KUMAR, solemnly declare that the dissertation titled **"CAROTID INTIMA MEDIA THICKNESS AS A MARKER OF CORONARY ARTERY DISEASE IN TYPE 2 DIABETES MELLITUS"** has been prepared by me. This is submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment of the regulations for the award of MD Degree Branch I (General Medicine). It was not submitted to the award of any degree/ diploma to any University either in part or in full form previously.

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ABBREVATIONS AND ACRONYMS

CIMT – Carotid Intima Media Thickness

CVA – Cerebero Vascular Accident

DM – Diabetes Mellitus

ADA – American Diabetes Association

IMT – Intima Media Thickness

CAD – Coronary Artery Disease

CVD – Cardio Vascular Disease

TMT – Tread Mill Testing

RWMA – Regional Wall Motion Abnormality

BP – Blood Pressure

ADA – American Diabetes Association

GTT – Glucose Tolerance Test

M – Male

F – Female

FBG – Fasting Blood Glucose

TC – Total Cholesterol

PVD – Peripheral Vascular Disease

IHD – Ischemic Heart Disease

CONTENTS

INTRODUCTION

Globally, more than half of the diabetic subjects die from coronary artery disease (CAD) [1]. Another large portion of the patients suffer from cerebral infarction and peripheral vascular disease, mainly due to markedly advanced atherosclerosis.

The U.K. Prospective Diabetes Study [2] and Finnish studies [3] have shown an association of the HbA1c level and the risk for CAD in type 2 diabetic patients.

Intima-media thickness (IMT) of the carotid artery has been used as a subclinical index of atherosclerosis [4–14]. Several studies have shown an association between increased carotid IMT and new myocardial infarction in elderly and middleaged subjects [13–14].

Study of carotid IMT in type 2 diabetic Asian subjects is of particular interest, because the prevalence and incidence of atherosclerotic vascular disease in the Asian general population is much higher than that in Western populations[15-16].

Cardiovascular events have been used as reliable end points for atherosclerosis intervention trials and epidemiological cohort studies. Ultrasonographic measurement of carotid artery intima-media thickness (IMT) allows the noninvasive and early detection of atherosclerotic changes and is used as a noninvasive end point for assessing the progression and regression of atherosclerosis in clinical trials [1-14,17]. It was previously reported that IMT was closely associated with not only the incidence of cerebrovascular disease, but also with that of coronary artery disease (CAD) in elderly and middle-aged subjects[13-14,18-20].

However, it has not been fully confirmed that IMT can be used as a predictor of CAD in diabetic patients. A few previous studies have evaluated the association between carotid IMT and CAD in patients with type 2 diabetes [8,20-21]. In these studies, CAD was diagnosed from symptoms and

clinical records rather than by objective testing for evidence of CAD. It has been reported that diabetic patients often have diffuse and multiple cardiovascular stenoses, despite having less symptoms than nondiabetic subjects. In fact, the onset of CAD may be a severe or fatal event in diabetic patients. The prognosis of cardiovascular events in diabetic patients tends to be worse than that in nondiabetic subjects. However, there is no general agreement regarding the best way to screen asymptomatic diabetic patients for significant CAD [20].

It is important to develop a simple method of detecting coronary artery disease at an early stage in diabetic patients. In the present study, we investigated the association between carotid atherosclerosis (measured from IMT) and CAD confirmed by Treadmill Testing and Echocardiography in patients with type 2 diabetes.

Various studies have shown that IMT increases mm/year in known cases of Cardiovascular disease (CVD) [22]. Hence IMT increase can be regarded as a marker of generalized atherosclerosis and atherosclerosis of coronary arteries [23,24]. On the other hand, IMT is related to coronary risk factors such as age, smoking, hypertension, and LDL-C [25]. In a number of recent studies, cholesterol lowering medications led to decrease in IMT [26-29]. These studies suggest that IMT is of high value as a marker of atherosclerosis. There have also been studies on the relationship between CAD and ultrasonographic variables with mixed results on how carotid IMT relates to CAD [30-33]. Individuals with atherosclerotic coronary arteries remain symptom-free for decades and the first manifestation of disease may be overwhelming, if not fatal, hence non-invasive ultrasonographic measurement of IMT can be of great value in screening for such asymptomatic patients. Preventing atherosclerosis and its progression remains a central goal in medicine [13].

In view of the high prevalence of CAD in our society and the fact that simple methods such as IMT measurement may detect atherosclerosis in its nascence and help prevent fatal events; this study was designed to assess the value of carotid IMT in predicting the risk of CAD. The objective of this study is to evaluate coronary atherosclerosis in type 2 diabetic subjects and measure their common carotid IMT, and to assess the relationship between the two parameters.

REVIEW OF LITERATURE

Definition and Demographics

ATHEROSCLEROSIS

Atherosclerosis is a multifactorial and dynamic process. One of its feature is the presence of fatty streaks along the vessel wall leading to build-up of plaques on the wall of arteries, which leads to reduction in caliber of vessels. Coronary artery disease (CAD) in India is reaching alarming and epidemic proportions [15,16].

DIABETES

India is frequently referred to as the diabetic capital of the world. Diabetes mellitus is widely prevalent in our country and its incidence is rising in alarming proportions.

According to the Diabetes Atlas published by the International Diabetes Federation (IDF), there are an estimated 40 million persons with diabetes in India in 2007 and this number is predicted to rise to almost 70 million people in 2025 by which time every fifth diabetic subject in the world would be an Indian.

The real burden of the disease is however due to its micro and macro vascular complications which lead to increased morbidity and mortality. Atherosclerotic vascular diseases, particularly Coronary artery diseases (CAD), are leading causes of morbidity and mortality amongst diabetics.

CORONARY ARTERY DISEASE

CAD causes more deaths and disability and incurs greater economic costs than any other illness in the developed world. Obesity, insulin resistance, and type 2 diabetes mellitus are

increasing and are powerful risk factors for CAD. With urbanization in the developing world, the prevalence of risk factors for CAD is increasing rapidly in these regions such that a majority of the global burden of CAD is now occurring in low-income and middle-income countries. Population subgroups that appear to be particularly affected are men in South Asian countries, especially India. Given the projection of large increases in CAD throughout the world, CAD is likely to become the most common cause of death worldwide by 2020.

Pathogenesis

ATHEROSCLEROSIS [40]

Atherosclerosis remains the major cause of death and premature disability in developed societies. Moreover, current predictions estimate that by the year 2020 cardiovascular diseases, notably atherosclerosis, will become the leading global cause of total disease burden.

Initiation of Atherosclerosis

An integrated view of experimental results in animals and studies of human atherosclerosis suggests that the "fatty streak" represents the initial lesion of atherosclerosis. These early lesions most often seem to arise from focal increases in the content of lipoproteins within regions of the intima. This accumulation of lipoprotein particles may not result simply from an increased permeability, or "leakiness," of the overlying endothelium . Rather, these lipoproteins may collect in the intima of arteries because they bind to constituents of the extracellular matrix, increasing the residence time of the lipid-rich particles within the arterial wall.

Leukocyte Recruitment

Accumulation of leukocytes characterizes the formation of early atherosclerotic lesions. Thus, from its very inception, atherogenesis involves elements of inflammation, a process that now provides a unifying theme in the pathogenesis of this disease. The inflammatory cell types typically found in the evolving atheroma include monocyte-derived macrophages and lymphocytes. A number of adhesion molecules or receptors for leukocytes expressed on the surface of the arterial endothelial cell likely participate in the recruitment of leukocytes to the nascent atheroma. Constituents of oxidatively modified low-density lipoprotein (LDL) can augment expression of leukocyte adhesion molecules. Once captured on the surface of the arterial endothelial cell by adhesion receptors, the monocytes and lymphocytes penetrate the endothelial layer and take up residence in the intima.

Foam Cell Formation

Once resident within the intima, the mononuclear phagocytes mature into macrophages and become lipid-laden foam cells, a conversion that requires the uptake of lipoprotein particles by receptor-mediated endocytosis.

Atheroma Evolution and Complications

Although the fatty streak commonly precedes the development of a more advanced atherosclerotic plaque, not all fatty streaks progress to form complex atheromata. By ingesting lipids from the extracellular space, the mononuclear phagocytes bearing such scavenger receptors may remove lipoproteins from the developing lesion. Some lipid-laden

macrophages may leave the artery wall, exporting lipid in the process. Lipid accumulation, and hence propensity to form atheroma, ensues if the amount of lipid entering the artery wall exceeds that removed by mononuclear phagocytes or other pathways.

The arrival of smooth-muscle cells and their elaboration of extracellular matrix probably provides a critical transition, yielding a fibrofatty lesion in place of a simple accumulation of macrophage-derived foam cells. Transforming growth factor beta, among other mediators, potently stimulates interstitial collagen production by smooth-muscle cells. These mediators hasten transformation of the fatty streak into a more fibrous smooth-muscle cell and extracellular matrix-rich lesion.

Calcification

As they advance, atherosclerotic plaques also accumulate *calcium*. Proteins usually found in bone also localize in atherosclerotic lesions, e.g., osteocalcin, osteopontin, and bone morphogenetic proteins.

Plaque Instability and Rupture

Postmortem studies afford considerable insight into the microanatomic substrate underlying the "instability" of plaques that do not cause critical stenoses. A superficial erosion of the endothelium or a frank plaque rupture or fissure usually produces the thrombus that causes episodes of unstable angina pectoris or the occlusive and relatively persistent thrombus that causes acute myocardial infarction. In the case of carotid atheromata, a deeper ulceration that provides a nidus for formation of platelet thrombi may cause transient cerebral ischemic attacks.

Prevention and Treatment

The Concept of Atherosclerotic Risk Factors

The systematic study of risk factors for atherosclerosis emerged from a coalescence of experimental results as well as cross-sectional and ultimately longitudinal studies in humans. The prospective, community-based Framingham Heart Study provided rigorous support for the concept that hypercholesterolemia, hypertension, and other factors correlated with cardiovascular risk. Similar observational studies performed worldwide bolstered the concept of "risk factors" for cardiovascular disease.

From a practical viewpoint, the cardiovascular risk factors that have emerged from such studies fall into two categories: those modifiable by lifestyle and/or pharmacotherapy and those such as age and gender that are immutable..

Major Risk Factors (Exclusive of LDL Cholesterol) that Modify LDL Goals [40]
Cigarette smoking
Hypertension (BP 140/90 mmHg or on antihypertensive medication)
Low HDL cholesterol[a] [<1.0 mmol/L (<40 mg/dL)]
Diabetes mellitus
Family history of premature CHD
CHD in male first-degree relative <55 years
CHD in female first-degree relative <65 years
Age (men 45 years; women 55 years)
Lifestyle risk factors
Obesity (BMI 30 kg/m^2)

Physical inactivity
Atherogenic diet
Emerging risk factors
Lipoprotein(a)
Homocysteine
Prothrombotic factors
Proinflammatory factors
Impaired fasting glucose
Subclinical atherogenesis

ISCHEMIC HEART DISEASE

Ischemic heart disease (IHD) is a condition in which there is an inadequate supply of blood and oxygen to a portion of the myocardium; it typically occurs when there is an imbalance between myocardial oxygen supply and demand. The most common cause of myocardial ischemia is atherosclerotic disease of an epicardial coronary artery (or arteries) sufficient to cause a regional reduction in myocardial blood flow and inadequate perfusion of the myocardium supplied by the involved coronary artery.

Pathophysiology

Central to an understanding of the pathophysiology of myocardial ischemia is the concept of myocardial supply and demand. Under normal conditions, for any given level of a demand for oxygen, the myocardium will be supplied with oxygen-rich blood to prevent underperfusion of myocytes and the subsequent development of ischemia and infarction. The

major determinants of myocardial oxygen demand (MVO_2) are heart rate, myocardial contractility, and myocardial wall tension (stress). An adequate supply of oxygen to the myocardium requires a satisfactory level of oxygen-carrying capacity of the blood (determined by the inspired level of oxygen, pulmonary function, and hemoglobin concentration and function) and an adequate level of coronary blood flow. Blood flows through the coronary arteries in a phasic fashion, with the majority occurring during diastole. About 75% of the total coronary resistance to flow occurs across three sets of arteries: (1) large epicardial arteries (Resistance 1 = R_1), (2) prearteriolar vessels (R_2), and (3) arteriolar and intramyocardial capillary vessels (R_3). In the absence of significant flow-limiting atherosclerotic obstructions, R_1 is trivial; the major determinant of coronary resistance is found in R_2 and R_3.

By reducing the lumen of the coronary arteries, atherosclerosis limits appropriate increases in perfusion when the demand for flow is augmented, as occurs during exertion or excitement. When the luminal reduction is severe, myocardial perfusion in the basal state is reduced.

Asymptomatic versus Symptomatic IHD

According to population studies, ~25% of patients who survive acute MI may not come to medical attention, and these patients carry the same adverse prognosis as those who present with the classic clinical picture of acute MI. Sudden death may be unheralded and is a common presenting manifestation of IHD.

Patients with IHD can also present with cardiomegaly and heart failure secondary to ischemic damage of the LV myocardium that may have caused no symptoms prior to the development of heart failure; this condition is referred to as *ischemic cardiomyopathy*. In contrast to the

asymptomatic phase of IHD, the symptomatic phase is characterized by chest discomfort due to either angina pectoris or acute MI. Having entered the symptomatic phase, the patient may exhibit a stable or progressive course, revert to the asymptomatic stage, or die suddenly.

Diagnosis :

Although the diagnosis of IHD can be made with a high degree of confidence from the clinical examination, a number of simple laboratory tests can be helpful. The urine should be examined for evidence of diabetes mellitus and renal disease (including microalbuminuria) since these conditions accelerate atherosclerosis. Similarly, examination of the blood should include measurements of lipids (cholesterol—total, LDL, HDL—and triglycerides), glucose, creatinine, hematocrit, and, if indicated based on the physical examination, thyroid function. A chest x-ray is important as it may show the consequences of IHD, i.e., cardiac enlargement, ventricular aneurysm, or signs of heart failure. These signs can support the diagnosis of IHD and are important in assessing the degree of cardiac damage.

Electrocardiogram

A 12-lead ECG recorded at rest may be normal in patients with typical angina pectoris, but there may also be signs of an old myocardial infarction. Although repolarization abnormalities—i.e., ST-segment and T-wave changes—as well as LV hypertrophy and intraventricular conduction disturbances are suggestive of IHD, they are nonspecific since they can also occur in pericardial, myocardial, and valvular heart disease or, in the case of the former, transiently with anxiety, changes in posture, drugs, or esophageal disease. Dynamic ST-segment and T-wave changes that accompany episodes of angina pectoris and disappear

thereafter are more specific.

Stress Testing [36] - Electrocardiographic stress test

The most widely used test for both the diagnosis of IHD and estimating the prognosis involves recording the 12-lead ECG before, during, and after exercise, usually on a treadmill. The test consists of a standardized incremental increase in external workload while the symptoms, ECG, and arm blood pressure are monitored. Performance is usually symptom-limited, and the test is discontinued upon evidence of chest discomfort, severe shortness of breath, dizziness, severe fatigue, ST-segment depression >0.2 mV (2 mm), a fall in systolic blood pressure >10 mmHg, or the development of a ventricular tachyarrhythmia. This test seeks to discover any limitation in exercise performance, to detect typical ECG signs of myocardial ischemia, and to establish their relationship to chest discomfort. The ischemic ST-segment response is generally defined as flat or downsloping depression of the ST segment >0.1 mV below baseline (i.e., the PR segment) and lasting longer than 0.08 s. Upsloping or junctional ST-segment changes are not considered characteristic of ischemia and do not constitute a positive test. Although T-wave abnormalities, conduction disturbances, and ventricular arrhythmias that develop during exercise should be noted, they are also not diagnostic. Negative exercise tests in which the target heart rate (85% of maximal predicted heart rate for age and sex) is not achieved are considered to be nondiagnostic.

When interpreting ECG stress tests, the probability that coronary artery disease (CAD) exists in the patient or population under study (i.e., pretest probability) should be considered.

Overall, false-positive or false-negative results occur in one-third of cases. However, a positive result on exercise indicates that the likelihood of CAD is 98% in males >50 years with a history of typical angina pectoris and who develop chest discomfort during the test. The likelihood decreases if the patient has atypical or no chest pain by during the test.

The incidence of false-positive tests is significantly increased in patients with low probabilities of IHD, such as asymptomatic men under the age of 40 or in premenopausal women with no risk factors for premature atherosclerosis. It is also increased in patients taking cardioactive drugs, such as digitalis and antiarrhythmic agents, or in those with intraventricular conduction disturbances, resting ST-segment and T-wave abnormalities, ventricular hypertrophy, or abnormal serum potassium levels. Obstructive disease limited to the circumflex coronary artery may result in a false-negative stress test since the lateral portion of the heart which this vessel supplies is not well represented on the surface 12-lead ECG. Since the overall sensitivity of exercise stress electrocardiography is only ~75%, a negative result does not exclude CAD, although it makes the likelihood of three-vessel or left main CAD extremely unlikely.

Contraindications to exercise stress testing include rest angina within 48 h, unstable rhythm, severe aortic stenosis, acute myocarditis, uncontrolled heart failure, severe pulmonary hypertension, and active infective endocarditis.

Cardiac Imaging

When the resting ECG is abnormal (e.g., preexcitation syndrome, >1 mm of resting ST-segment depression, left bundle branch block, paced ventricular rhythm), information gained from an exercise test can be enhanced by stress myocardial radionuclide perfusion imaging after the intravenous administration of thallium 201 or technetium 99m (^{99m}Tc) sestamibi

during exercise (or a pharmacologic) stress.

Two-dimensional echocardiography can assess both global and regional wall motion abnormalities of the left ventricle due to MI or persistent ischemia. Stress (exercise or dobutamine) echocardiography may cause the emergence of regions of akinesis or dyskinesis not present at rest. Stress echocardiography, like stress myocardial perfusion imaging, is more sensitive than exercise electrocardiography in the diagnosis of IHD.

Atherosclerotic plaques become progressively calcified over time, and coronary calcification in general increases with age. For this reason, methods for detecting coronary calcium have been developed as a measure of the presence of coronary atherosclerosis. Coronary calcium detected by these imaging techniques is quantified using the Agatston score most commonly, which is based on the area and density of calcification. Although the diagnostic accuracy of this imaging method is high (sensitivity, 90–94%; specificity, 95–97%; negative predictive value, 93–99%), its prognostic utility and its role in the evaluative algorithm of patients with stable angina pectoris have not yet been defined.

Coronary Arteriography

This diagnostic method outlines the lumina of the coronary arteries and can be used to detect or exclude serious coronary obstruction. However, coronary arteriography provides no information regarding the arterial wall, and severe atherosclerosis that does not encroach on the lumen may go undetected. Of note, atherosclerotic plaques characteristically grow progressively in the intima and media of an epicardial coronary artery, at first without encroaching on the lumen, causing an outward bulging of the artery—a process referred to as negative remodeling.Later in the course of the disease, further growth causes luminal

narrowing.

Prognosis of IHD

The principal prognostic indicators in patients known to have IHD are age, the functional state of the left ventricle, the location(s) and severity of coronary artery narrowing, and the severity or activity of myocardial ischemia. Angina pectoris of recent onset, unstable angina[(40)] , early postmyocardial infarction angina, and angina that is unresponsive or poorly responsive to medical therapy or is accompanied by symptoms of congestive heart failure all indicate an increased risk for adverse coronary events. The same is true for the physical signs of heart failure, episodes of pulmonary edema, transient third heart sounds, or mitral regurgitation, and for echocardiographic or radioisotopic (or roentgenographic) evidence of cardiac enlargement and reduced (<0.40) ejection fraction.

Most importantly, any of the following signs during noninvasive testing indicate a high risk for coronary events: inability to exercise for 6 min, i.e., stage II (Bruce protocol) of the exercise test; a strongly positive exercise test showing onset of myocardial ischemia at low workloads (0.1 mV ST-segment depression before completion of stage II; 0.2 mV ST depression at any stage; ST depression for >5 min following the cessation of exercise; a decline in systolic pressure >10 mmHg during exercise; the development of ventricular tachyarrhythmias during exercise); the development of large or multiple perfusion defects or increased lung uptake during stress radioisotope perfusion imaging; and a decrease in LV ejection fraction (LVEF) during exercise on radionuclide ventriculography or during stress echocardiography. Conversely, patients who can complete stage III of the Bruce exercise protocol and have a normal stress perfusion scan or negative stress echocardiographic evaluation are at very low risk of future coronary events.

The greater the number and severity of risk factors for coronary atherosclerosis [advanced age (>75 years), diabetes, morbid obesity, accompanying peripheral and/or cerebrovascular disease, previous MI], the worse the prognosis of the angina patient. Evidence exists that elevated levels of increased carotid intimal thickening on ultrasound examination indicate an increased risk of coronary events.

Stable Angina Pectoris: Treatment [37]

The management plan should include the following components: (1) explanation of the problem and reassurance about the ability to formulate a treatment plan, (2) identification and treatment of aggravating conditions, (3) recommendations for adaptation of activity as needed, (4) treatment of risk factors that will decrease the occurrence of adverse coronary outcomes, (5) drug therapy for angina, and (6) consideration of revascularization [38] with either Percutaneous coronary intervention [39] or Coronary artery bypass grafting.

Asymptomatic (Silent) Ischemia

Obstructive CAD, acute MI, and transient myocardial ischemia are frequently asymptomatic. During continuous ambulatory ECG monitoring, the majority of ambulatory patients with typical chronic stable angina are found to have objective evidence of myocardial ischemia (ST-segment depression) during episodes of chest discomfort while they are active outside the hospital, but many of these patients have more frequent episodes of asymptomatic ischemia. In addition, there is a large (but as yet unknown) number of totally asymptomatic persons with severe coronary atherosclerosis who exhibit ST-segment changes during

activity.

Frequent episodes of ischemia (symptomatic and asymptomatic) during daily life appear to be associated with an increased likelihood of adverse coronary events (death and MI). In addition, patients with asymptomatic ischemia after suffering a myocardial infarction are at greater risk for a second coronary event. The widespread use of exercise ECG during routine examinations has also identified some of these heretofore unrecognized patients with asymptomatic CAD. Longitudinal studies have demonstrated an increased incidence of coronary events in asymptomatic patients with positive exercise tests [44-47] .

Asymptomatic Ischemia: Treatment [37]

The management of patients with asymptomatic ischemia must be individualized. Thus, the physician should consider the following: (1) the degree of positivity of the stress test, particularly the stage of exercise at which ECG signs of ischemia appear, the magnitude and number of the ischemic zones of myocardium on imaging, and the change in LVEF which occurs on radionuclide ventriculography or echocardiography during ischemia and/or during exercise; (2) the ECG leads showing a positive response, with changes in the anterior precordial leads indicating a less favorable prognosis than changes in the inferior leads; and (3) the patient's age, occupation, and general medical condition.

The treatment of risk factors, particularly lipid lowering as described above, and the use of aspirin, beta blockers, and statins have been shown to reduce events and improve outcomes in asymptomatic as well as symptomatic patients with ischemia and proven CAD. While the incidence of asymptomatic ischemia can be reduced by treatment with beta blockers, calcium channel blockers, and long-acting nitrates, it is not clear whether this is necessary or desirable in patients who have not suffered a myocardial infarction.

DIABETES MELLITUS

Diabetes mellitus (DM) refers to a group of metabolic disorders which have a common denominator namely hyperglycemia. Factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system.[40]

Classification

DM is classified on the basis of the pathogenic process that leads to hyperglycemia. The two broad categories of DM are designated type 1 and type 2.

- Type 1 diabetes is the result of complete or near-total insulin deficiency.

- Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. Type 2 DM is preceded by a period of abnormal glucose homeostasis classified as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).

Pathophysiology

Type 2 DM is characterized by impaired insulin secretion, insulin resistance, excessive hepatic glucose production, and abnormal fat metabolism. Obesity, particularly visceral or central (as evidenced by the hip-waist ratio), is very common in type 2 DM. In the early stages of the disorder, glucose tolerance remains near-normal, despite insulin resistance, because the pancreatic beta cells compensate by increasing insulin output. As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets in certain

individuals are unable to sustain the hyperinsulinemic state. IGT, characterized by elevations in postprandial glucose, then develops. A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycemia. Ultimately, beta cell failure may ensue.

Chronic Complications of DM

The chronic complications of DM affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. Chronic complications can be divided into vascular and nonvascular complications. The vascular complications of DM are further subdivided into microvascular (retinopathy, neuropathy, nephropathy) and macrovascular complications [coronary artery disease (CAD), peripheral arterial disease (PAD), cerebrovascular disease].

The microvascular complications of both type 1 and type 2 DM result from chronic hyperglycemia. Large, randomized clinical trials of individuals with type 1 or type 2 DM have conclusively demonstrated that a reduction in chronic hyperglycemia prevents or delays retinopathy, neuropathy, and nephropathy.

Evidence implicating a causative role for chronic hyperglycemia in the development of macrovascular complications is less conclusive. However, coronary heart disease events and

mortality are two to four times greater in patients with type 2 DM. These events correlate with fasting and postprandial plasma glucose levels as well as with the A1C. Other factors (dyslipidemia and hypertension) also play important roles in macrovascular complications.

Mechanism of Complications

Although chronic hyperglycemia is an important etiologic factor leading to complications of DM, the mechanism(s) by which it leads to such diverse cellular and organ dysfunction is unknown. Four prominent theories, which are not mutually exclusive, have been proposed to explain how hyperglycemia might lead to the chronic complications of DM. One theory is that increased intracellular glucose leads to the formation of advanced glycosylation end products (AGEs) via the nonenzymatic glycosylation of intra- and extracellular proteins, sorbitol pathway, phosphokinase C pathway and hexosaminase pathway being the other three postulates.

CAROTID INTIMA MEDIA THICKNESS

Two decades ago investigators showed that the thickness of the carotid wall (intima and media layer taken together) measured ultrasonographically was associated with the presence and extent of atherosclerosis of the aorta [5,41]. Due to the limited resolution of the ultrasound equipment the intima cannot be differentiated from the media. Nonetheless, several randomized and epidemiological studies clearly proved the value of the CIMT as a marker of CVD risk. An increased CIMT has been associated with risk of MI and CVA in the elderly (> 65 years) [14] as well as younger age groups. Furthermore, it was recently shown that CIMT adds incremental prognostic information to traditional risk factors for the prediction of coronary events in asymptomatic patients with type 2 diabetes. Of note, there is only a modest relationship between CIMT and obstructive CAD in non-diabetic, as well as diabetic

subjects [13] . This clearly suggests that CIMT is a marker of atherosclerosis burden rather than a surrogate for obstructive CAD.

Increased CIMT in diabetes has been associated with risk factors for atherosclerosis such as high serum triglyceride levels and low total/HDL cholesterol ratio,LDL [42,43] , age, BMI, Lp(a), microalbuminuria, as well as endothelial dysfunction and low grade inflammation. Insulin resistance alone in the absence of clinical diabetes has been associated with an increased CIMT. Sequential CIMT measurements have demonstrated that diabetes is an independent predictor of CIMT progression [9] .

Furthermore, CIMT appears to progress faster in diabetic patients than in all other patients. In IRAS, the investigators enrolled 1,192 men and women with normal or IGT and fulminant type 2 diabetes. Participants with diabetes showed the fastest CIMT progression during the five-year follow- up. In non-diabetic subjects, common and internal carotid artery CIMT progressed by 3.8 and 17.7 μm/year, respectively and no significant difference was noted between patients with normal glucose tolerance or IGT. Diabetic subjects showed a two-fold greater progression of both common and internal carotid artery CIMT. Glycaemic control (both fasting glucose levels and HbA1C) were at least in part responsible for such accelerated progression.

B-mode ultrasound is a relatively inexpensive and safe technique that can noninvasively visualize the vessel lumen. B-mode ultrasound has been validated for measuring intima-media thickness (IMT) in several independent laboratories, and its reliability has been established in single- and multicenter studies. Current ultrasound instrumentation with transducers 4-8 MHz are most capable of identifying the 2 arterial interfaces (lumen-intima and media-adventitia) necessary for measuring IMT. The screening examination is performed bilaterally on the extracranial carotid artery segments. These segments are the distal straight 1 cm of the common carotid arteries, the carotid bifurcations,

and the proximal 1 cm of the internal carotid arteries. Circumferential longitudinal scans can identify IMTs on the near and far walls of each segment (total of 6 walls per side). The actual thickness of each lesion is measured with ultrasound instrument calipers. IMT is an operational measurement definition of a single characteristic of atherosclerosis based on considerable information documenting that both the intima and media are involved in atherogenesis and the anatomical progression of lesions.

Common carotid IMT has been associated with prevalent cardiovascular disease in cross-sectional studies [45–47] . Furthermore, various published studies found that carotid IMT measurement is a viable predictor of the presence of coronary atherosclerosis and its clinical sequelae [44,45-47] . Thus, carotid IMT defined by noninvasive B-mode ultrasound has been shown to be an independent risk factor for CAD events and stroke. The strongest data relating IMT measurement with incident cardiovascular events derive from the Atherosclerosis Risk in Communities (ARIC) Study [12] .

Several clinical intervention or prevention trials have illustrated the ability of carotid B-mode ultrasound imaging to monitor changes in IMT over time. Although serial measurements can be standardized in well-controlled research settings, protocols for sonographers to monitor IMT over time in a valid and reliable manner have not yet been implemented in clinical practice environments.

To assess the regression or progression of atherosclerosis in intervention trials. IMT measurement is the best-established, and longitudinal studies have presented the regression of atherosclerosis by lipidlowering with statins .This was evident from the trials conducted by Furberg CD et al. Effects of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. Circulation 1994; 90:1679–87 and Groot Eet al ; Effects of pravastatin on progression and regression of coronary atherosclerosis and vessel wall changes in carotid and femoral arteries:

a report form the Regression Growth Evaluation Statin Study. Am J Cardiol 1995; 76:40–6.

AIM OF THE STUDY

1. To find out the prevalence of coronary artery disease in asymptomatic type 2 diabetes mellitus patients by treadmill test.

2. To estimate subclinical atherosclerosis in patients with type 2 diabetes mellitus by measuring the carotid intima media thickness.

3. To find the association between carotid intima media thickness and coronary artery disease in asymptomatic patients with type 2 diabetes mellitus.

4. To study the association of age, sex, body mass index, smoking, alcohol, duration of diabetes, hypertension, fasting hyperglycemia, serum total cholesterol, diabetic

retinopathy, nephropathy and peripheral vascular disease with the carotid intima media thickness.

MATERIALS AND METHODS

Setting:

The study was conducted on type 2 diabetic patients attending the out patient department of Government Rajaji Hospital, Madurai.

Design of study: The study was a cross sectional case-control analytical study.

Period of study: The study was conducted from June 2007 to November 2008.

Ethical committee approval: Approval from the hospital ethical committee was obtained.

Consent : Informed consent was obtained from the subjects studied.

Criteria for selection of subjects: Rigid criteria were adopted for inclusion and exclusion of cases and controls for the present study. The details are furnished below.

Inclusion criteria:

Asymptomatic individuals attending the outpatient department of medicine and diabetology diagnosed with type 2 diabetes mellitus according to ADA 2007 criteria were included in the study if they met the following inclusion criteria.

1) no episodes of ketoacidosis and absence of ketonuria,

2) diagnosis of diabetes after 30 years of age,

3) insulin therapy (if any) started after at least 5 years after diagnosis and

5) absence of acute stage or signs and symptoms of CHD / cerebral vascular disease after careful evaluation of clinical records.

Type 2 diabetes mellitus cases with evidence of previous MI either with ECG evidence of STEMI or echocardiography showing regional wall motion abnormality were also included to avoid selection bias and to act as positive controls in order to assess the strength of association.

The determination of type 2 diabetes was based on ADA 2007 criteria, which defines the diagnosis of Diabetes Mellitus as follows:

1. Symptoms of diabetes plus random blood glucose>200mg/dl (or)
2. Fasting plasma glucose>126mg/dl (or)
3. Two-hour plasma glucose>200mg/dl during an oral GTT.

Exclusion criteria:

1. Those having acute metabolic complications like hypoglycemia, diabetic ketoacidosis, hyperosmolar hyperglycaemic state, cerebrovascular accidents, acute infections, inherited disorders of lipid and lipoprotein metabolism and/or family history of such disorders and deranged liver functions were excluded.
2. Patients on lipid lowering treatment
3. Previous history of CABG or PCI intervention.

4. Contraindications to exercise stress testing which include rest angina within 48 h, unstable rhythm, severe aortic stenosis, acute myocarditis, uncontrolled heart failure, severe pulmonary hypertension, and active infective endocarditis.

Subjects: Thus a total of 50 cases that satisfied the inclusion and exclusion criteria stated above were taken up for the study. 15 cases of type 2 diabetics with MI served as positive controls to provide corroborative evidence of the strength of association and to eliminate selection bias.

Controls : Fifteen (10 males and 5 females) age, sex and BMI matched non-diabetic subjects with no evidence of cardiovascular, cerebrovascular or peripheral vascular disease or their risk factors were recruited as controls.

Study protocol: Patients attending the outpatient department of diabetology or medicine in Government Rajaji Hospital were the study group. A well designed proforma was used to collect the demographic and clinical details of the patients.

Collaborating departments:

Department of Medicine, Madurai Medical College, Madurai

Department of Cardiology, Madurai Medical College, Madurai

Department of Diabetology, Madurai Medical College, Madurai

Department of Vascular Surgery, Madurai Medical College, Madurai.

METHODS: Selected sociodemographic, clinical and laboratory data were collected from both the cases and controls and were recorded in a pro forma.

Socio demographic data comprised of:

- age
- sex
- locality
- occupation

Clinical data comprised of:

- History of Diabetes, hypertension
- History of smoking, alcohol
- Height, weight and BMI
- General and systemic examination
- Fundus examination
- Examination of peripheral pulses and BP recording in all 4 limbs with Ankle-Brachial Index (ABI) calculated from the BP values.

Laboratory data included:

- Urine - albumin, deposits, Sugar
- Fasting Blood Sugar
- Blood Urea
- Serum Creatinine
- Fasting Serum Total Cholesterol
- ECG

Imaging studies

- TMT
- Echocardiography
- CAROTID INTIMA MEDIA THICKNESS by Doppler

65 consecutive type 2 diabetic patients (diagnosed by the World Health Organization criteria) among the outpatients attending departments of medicine and diabetology were subjected to detailed history, physical examination, BP recording in all 4 limbs, examination

of all peripheral pulses, height, weight and calculated BMI(weight in kg / height in metre square).Baseline laboratory data, resting 12-lead ECG, TMT, Echocardiography, and CIMT measurement were collated for each patient. Fasting blood sample was obtained, and measurement of serum total cholesterol, serum creatinine, blood urea, and blood sugar was made by standard laboratory techniques. A single morning urine sample was obtained and was tested for the presence of albumin by heat coagulation method.

Blood pressure was measured with a standard mercury sphygmomanometer after the subject had been seated for at least 5 min. Hypertension was defined as a systolic blood pressure >140 mmHg, a diastolic blood pressure >90 mmHg, and/or the use of antihypertensive medication in accordance with JNC VII criteria.

CAD was diagnosed based on combinations of symptoms, resting electrocardiogram (ECG) changes, positive TMT result and echocardiographic evidence of regional wall motion abnormality (RWMA) suggestive of CAD.

Screening for silent myocardial ischemia was performed on the remaining patients. Exercise ECG in the form of Tread Mill Testing (TMT) was the choice for screening method. Modified Bruce Protocol was performed in 50 randomly selected type 2 diabetic patients.

Hyperlipidemia was considered present when the patient had a serum total cholesterol level >200 mg/dl.

Ankle-Brachial Index (ABI) was considered to be positive if the patient had ratio of systolic BP in ankle to that of the arm less than 1 in either of the limbs.Peripheral vascular disease (PVD) was considered to be positive if any of the cases had showed a positive ABI.

The criterion for diagnosis of diabetic retinopathy was the presence of at least one definite microaneurysm in any field of the eye. Briefly, level 10 represents no

retinopathy, levels 20–50 nonproliferative diabetic retinopathy, and level >60proliferative diabetic retinopathy.

The presence of a positive albumin test in urinalysis was taken as evidence of diabetic nephropathy.

Tread Mill Testing (TMT) :

The most widely used test for both the diagnosis of IHD and estimating the prognosis involves recording the 12-lead ECG before, during, and after exercise, usually on a treadmill. The test consists of a standardized incremental increase in external workload ,while the symptoms, ECG, and arm blood pressure are monitored.

Positive TMT result :

The ischemic ST-segment response is generally defined as flat or downsloping depression of the ST segment >0.1 mV below baseline (i.e., the PR segment) and lasting longer than 0.08 s.

Negative TMT result :

Upsloping or junctional ST-segment changes are not considered characteristic of ischemia and do not constitute a positive test. Negative exercise tests in which the target heart rate (85% of maximal predicted heart rate for age and sex) is not achieved are considered to be nondiagnostic.

ECHOCARDIOGRAPHY :

Two-dimensional echocardiography to assess both global and regional wall motion abnormalities of the left ventricle due to MI were taken as evidence of CAD.

Echocardiography was also done to rule out contraindications to exercise stress testing include severe aortic stenosis, acute myocarditis, uncontrolled heart failure, severe pulmonary hypertension, and active infective endocarditis.

ASSESSMENT OF CAROTID INTIMA MEDIA THICKNESS :

Ultrasonographic scanning of the carotid arteries was performed using WIPRO – Ge logic 400 MD scanner with a linear transducer (midfrequency range 7.5–10 MHz). The patient being in supine position and chest being elevated with a pillow and the head being turned to the opposite side of the carotids examined. The probe was placed on the medial side of the sternocleidomastoid muscle to identify the carotid vessel and the carotid bulb was traced. Intima media thickness was assessed at about 1.0 cm proximal to the carotid bulb. The carotid wall shows parallel echogenic lines separated by a hypoechoic region (media). The inner line is the lumen – intima interface and the outer is the media – adventitia interface.

Carotid IMT was defined as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line on the scans. Carotid IMT was measured on both sides and the average value was taken as the mean CIMT.IMT value of more than 0.8 mm is suggestive of significant atherosclerosis [53] .

Conflict of interest: There was no conflict of interest.

Financial support: Nil.

Statistical analysis:

The information collected regarding all the selected cases were recorded in a Master Chart in Microsoft Excel spreadsheet. Data analysis was done with the help of computer using **Epidemiological Information Package (EPI 2002).**

Using this software, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables and Yate's test for qualitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

Observations and Results

Profile of Total Cases studied :

Majority of the patients were from in and around Madurai city. The total number of patients included in the study was 65. Fifteen controls were also included in the study for comparative analysis.

Patients were divided into three groups :

GROUP I (NON-CAD) - Type 2 diabetics who were screened for silent ischemia by TMT and echocardiography, who showed negative results for CAD .

GROUP II (CAD) - Type 2 diabetics subclassified into those who showed evidence of CAD in the form of either a positive TMT result (IHD) or echocardiographic evidence of RWMA (MI).

GROUP III (CONTROL) – Age , sex and BMI matched non-diabetics

Among the total of 65 Type 2 diabetes mellitus patients, **23 diabetic patients [Female (F)-5; Male (M)-18]** had no evidence of CAD (**Group-I**), whereas **42 diabetic patients (F-9; M-33)** had evidence of CAD (**Group-II**). Among the group II cases, 27 cases were asymptomatic (IHD) and the rest 15 were symptomatic (MI).

Out of the 15 controls **(Group-III),** 10 were male and 5 were female. They had no evidence of diabetes or its complications after clinical and laboratory evaluation.

The age distribution of the patients is shown in table 1.

COMPARISON OF PARAMETERS IN THE THREE GROUPS

Table 1 : Age distribution

Age group	**Group I**		**Group II**		**Group III**	
	No	**%**	**No**	**%**	**No**	**%**
Less than 40	2	8.7	1	2.4	-	-
40-60	21	91.3	34	81	15	100
>60	-	-	7	16.7	-	-

Total	23	100	42	100	15	100
Mean	48.8 yrs		52.4 yrs		50.3 yrs	
SD	7.4 yrs		8 yrs		5.4 yrs	
'p'	0.2135 Not Significant					

The age of the patients in group I ranged from 33-60 years with a mean of 48.8±7.4 years, while that of group II ranged from 34-65 years with a mean of 50.3±5.4 years. The age of the controls ranged from 45 to 60 years with a mean age of 50.3±5.4 years. Twenty one patients in group I (91.3%) and thirty four patients in group II (81%) were in the age group of 40-60 years.

The age groups of all the three groups were comparable and there was no statistical difference (p=0.2135).

Table 2 : Sex Distribution

Sex	**Group I**		**Group II**		**Group III**	
	No	**%**	**No**	**%**	**No**	**%**
Males	18	78.3	33	78.6	10	66.7
Females	5	21.7	9	21.4	5	33.3
Total	23	100	42	100	15	100

It was observed that there were 18 males and 5 females in Group I, 33 males and 9 females in Group II, 10 males and 5 females in Group III.

Table 3 : Duration of DM

Parameter	**Group I**		**Group II**		**Group III**	
	No	**%**	**No**	**%**	**No**	**%**
Duration of DM						
<10 years	15	65.2	12	28.6	-	-
10-15 years	4	17.4	18	42.9	-	-

Parameter	Group I		Group II		Group III	
	No	%	No	%	No	%
>15 years	4	17.4	12	28.6	-	-

Of the 23 cases in Group I, 65.2% of them had duration of DM <10 years compared to 28.6% in group II,17.4% had DM for 10-15years compared to 42.9% in group II and 17.4% had DM for>15 years compared to 28.6% of cases in group II.

Table 4: Prevalence of Hypertension

Parameter	Group I		Group II		Group III	
	No	%	No	%	No	%
Hypertension						
Present	5	21.7	21	50	-	-
Absent	18	78.3	21	50	15	100

In our study, hypertension was present in 5 cases (21.7 %) in group I and 21 cases (50%) in group II.

Table 5 : Prevalence of Smoking

Parameter	Group I		Group II		Group III	
	No	%	No	%	No	%

Parameter	Group I		Group II		Group III	
	No	%	No	%	No	%
Smoking among males						
Yes	7	38.9	19	45.5	5	33
No	16	61.1	23	54.5	10	67

The table shows that 38.9% of group I males and 45.5% of group II males were smokers.

Table 6: Prevalence of Alcoholism

Parameter	Group I		Group II		Group III	
	No	%	No	%	No	%
Alcoholism						
Yes	10	43.5	16	38.1	5	33
No	13	56.5	26	61.9	10	67

In our study ,26 cases (32.5%) in total were alcoholics, out of which 10 cases belonged to group I and 16 cases belonged to group II. All alcoholics were males.

Table 7 : BMI

BMI	Group I	Group II	Group III
Mean	26.4	27.4	25.6
SD	3.1	3.1	3.1
'P'	0.1124 Not Significant		

The BMI of the three groups was comparable and there was no statistical difference (p=0.1124).

Table 8: Fasting Blood Sugar

FBS	Group I	Group II	Group III
Mean	185.0	193.2	94.2
SD	42	49.3	12.9
'p'	**0.0001 Significant**		

Mean fasting blood glucose was 185± 42 mg/dl in group I compared to 193.2±49.3 mg/dl in group II and 94.2±12.9 mg/dl in group III.

The FBG of the three groups showed significant difference (p=0.0001), cases with CAD showing higher mean FBG values.

Table 9: Total Cholesterol

Total Cholesterol	Group I	Group II	Group III
Mean	193.8	214.6	180.1
SD	32.2	32.6	21.3
'P'	**0.0008 Significant**		

The fasting serum total cholesterol values in the three groups had a mean of 193.8±32.2 mg/dl in group I, 214.6±32.6 mg/dl in group II and 180.1±21.3 mg/dl in group III respectively.

There was statistically significant difference (p=0.0008) in the TC values between the three groups, diabetics with evidence of CAD having significantly higher prevalence of hypercholesterolemia compared to diabetics without CAD and non-diabetic controls.

Table 10 : Prevalence of Retinopathy

Parameter	Group I		Group II		Group III	
	No	%	No	%	No	%
Retinopathy						
Yes	3	13	19	45.2	-	-
No	20	87	23	54.8	15	100

In our study, retinopathy was present in 22 cases totally, out of which 3 cases (13%) were in group I and in 19 cases (45.2%) were in group II.

Table 11 : Prevalence of Nephropathy

Parameter	Group I		Group II		Group III	
	No	%	No	%	No	%
Nephropathy						
Yes	2	8.7	9	21.4	-	-
No	21	91.3	33	78.6	15	100

Our study shows that, 11 cases (13.8% prevalence) had evidence of diabetic nephropathy in total. 2 cases were in group I and the remaining 9 cases belonged to group II.

Table 12 : Prevalence of PVD

Parameter	Group I		Group II		Group III	
	No	%	No	%	No	%
PVD						
Yes	2	8.7	8	19	-	-
No	21	91.3	34	81	15	100

The above table from our study shows that there were 10 cases(12.5% prevalence) of PVD in diabetics. Of this, 2 cases belonged to group I and 8 cases belong to group II.

Table 13 : Prevalence of CAD

Parameter	Asymptomatic Diabetics	
	No	%
CAD		
Positive (GroupII)	27	54
Negative (Group I)	23	46

Our study showed 54% prevalence of CAD among asymptomatic type 2 diabetics.

Table 14: Carotid Intima Media Thickness and Coronary Artery Disease

CIMT	Group I	Group II	Group III
Mean	0.79	1.33	0.59
SD	0.35	0.52	0.1

Group I and Group III – 'p' value 0.0941 (Not significant)

Group II and Group III – 'p' value 0.0001 (Significant)

Group I and Group II – 'p' value 0.0001 (Significant)

The mean value of CIMT was 0.79±0.35 mm in group I, 1.33±0.52 mm in group II and 0.59±0.1 mm in group III respectively. The mean CIMT among diabetics was 1.06 ±0.43mm.

There was statistically significant difference in CIMT between the CAD group with Non-CAD group and controls.

There was no significant difference in CIMT value between Non-CAD group and controls.

Table 15 : CIMT in Asymptomatic Diabetic with CAD compared to MI cases

Parameter	CIMT		'p'
	Mean	SD	
Asymptomatic CAD Group	1.22	0.5	0.0544 Not Significant
MI Group	1.53	0.51	

Table 16 : CIMT in Asymptomatic Diabetics with CAD compared to controls

Parameter	CIMT		'p'
	Mean	SD	
Asymptomatic CAD Group	1.22	0.5	0.0001 **Significant**
Controls	0.59	0.1	

Mean CIMT was high in diabetics with Asymptomatic CAD (1.22mm) and MI cases (1.53 mm).The difference was not statistically significant between the groups(p=0.0544). The results thus show that CIMT was associated with CAD in established MI cases as well as in asymptomatic diabetics.

When compared to controls, mean CIMT was significantly associated with asymptomatic CAD group (p=0.0001).

RELATIONSHIP OF CIMT WITH OTHER PARAMETER IN THE 3 GROUPS

Table 17 : Age and CIMT

Age group	**CIMT**					
	Group I		**Group II**		**Group III**	
	No	**SD**	**No**	**SD**	**No**	**SD**
<40	0.5	-	0.5	-	-	-
40-60	0.82	0.35	1.3	0.54	0.59	0.1
>60	-	-	1.61	0.25	-	-
'p'	0.0979 Not Significant		**0.0032** **Significant**		-	

There was significant difference in the mean CIMT when compared with age between group I (p=0.0979) and group II (p=0.0032).

Table 18 : Sex and CIMT

Sex	**CIMT Value in Group**					
	Group I		**Group II**		**Group III**	
	No	**SD**	**No**	**SD**	**No**	**SD**
Males	0.83	0.36	1.35	0.52	0.58	0.1
Female	0.66	0.27	1.26	0.57	0.62	0.11
'p'	0.3089 Not Significant		0.7234 Not Significant		0.6081 Not Significant	

Mean CIMT values between males and females were 0.83 and 0.66mm in group I (p=0.3089), 1.35 and 1.26 mm in group II (p=0.7234), 0.58 and 0.62mm in group III (p=0.6081) respectively.

There was no significant difference in CIMT values between both sexes of the same group.

Table 19 : Duration of DM and CIMT

Duration of DM	CIMT					
	Group I		Group II		Group III	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
< 10 yrs	0.64	0.18	0.88	0.44	-	-
10-15 yrs	0.85	0.39	1.38	0.37	-	-
>15yrs	1.3	0.36	1.7	0.5	-	-
'p'	**0.0136 Significant**		**0.0003 Significant**		-	

From the table, it is evident that CIMT was maximum in patients who had longer duration of DM in group I (p=0.0136) and group II (p=0.0003).

Table 20 : Hypertension and CIMT

Hypertension	CIMT					
	Group I		Group II		Group III	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Present	1.12	0.46	1.61	0.46	-	-
Absent	0.7	0.25	1.05	0.43	0.59	0.1
'p'	**0.0237 Significant**		**0.0032 Significant**		-	

This table shows that CIMT is significantly associated with the prevalence of hypertension in diabetics belonging to the Non-CAD group (p=0.0237) and the CAD group (p=0.0032).

Table 21 : Smoking and CIMT

Smoking	CIMT					
	Group I		Group II		Group III	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Yes	0.83	0.19	1.45	0.51	0.63	0.12
No	0.69	0.39	0.86	0.52	0.61	0.1
'p'	0.7611 Not significant		**0.01518** **Significant**		0.6341 Not significant	

Our study shows that CIMT wass significantly associated with smoking in the CAD group (p=0.01518).

Table 22 : Alcoholism and CIMT

Alcoholism	CIMT					
	Group I		Group II		Group III	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Yes	0.75	0.28	1.46	0.49	0.64	0.12
No	0.82	0.4	1.25	0.54	0.58	0.1
'p'	0.95 Not significant		0.1936 Not significant		0.834 Not significant	

CIMT in alcoholics belonging to group I was 0.75 mm compared to 0.82 mm in non-alcoholics. The difference was not statisitically significant (p=0.95).

CIMT in alcoholics belonging to group II was 1.46 mm compared to 1.25 mm in non- alcoholics in that group. The difference was again not statistically significant (p=0.1936).

Table 23 : Fasting Blood Sugar and CIMT

FBS	CIMT for					
	Group I		Group II		Group III	
	No	SD	No	SD	No	SD
Normal (<126)	0.63	0.06	0.97	0.66	0.59	0.1
Abnormal (>126)	0.82	0.36	1.36	0.51	-	-
'p'	0.579 Not Significant		**0.0034** **Significant**		-	

Group I & II – 'p' value is 0.0046

Mean CIMT for cases in CAD group showed a statistically significant association with fasting hyperglycemia (p=0.0046) compared to non-CAD group.

Table 24 :Total Cholesterol and CIMT

Total Cholestrol	CIMT					
	Group I		Group II		Group III	
	No	SD	No	SD	No	SD
Normal (<200)	0.59	0.1	0.97	0.45	0.57	0.09
Abnormal (>200)	1.1	0.37	1.6	0.4	0.7	0.1
'p'	**0.0016** **Significant**		**0.0002** **Significant**		0.0589 Not significant	

CIMT showed a statistically significant association with the prevalence of hypercholesterolemia in group I (p=0.0016)and group II (p=0.0002).

CIMT was significantly associated with hypercholesterolemia in diabetics with stronger association in diabetics with CAD.

Table 25: Retinopathy and CIMT

Retinopathy	CIMT for					
	Group I		Group II		Group III	
	No	SD	No	SD	No	SD
Present	1.4	0.36	1.56	0.44	-	-
Absent	0.7	0.24	1.14	0.52	0.59	0.1
'p'	0.0097 Significant		0.0112 Significant		-	

CIMT was significantly high with patients in group I (p=0.0097) and group II (p=0.0112) who had diabetic retinopathy.The table shows that CIMT has a significant association with the prevalence of diabetic retinopathy.

Table 26 : Nephropathy and CIMT

Nephropathy	CIMT for					
	Group I		Group II		Group III	
	No	SD	No	SD	No	SD
Present	1.55	0.35	1.76	0.31	-	-
Absent	0.72	0.25	1.22	0.51	0.59	0.1
'p'	0.0205 Significant		0.0081 Significant		-	

CIMT was higher in diabetics with nephropathy in group I and group II.

The association was significant in group I (p=0.0205) and group II (p=0.0081).

The result shows that CIMT was signifaicantly associated with the prevalence of nephropathy in diabetics.

Table 27: PVD and CIMT

PVD	CIMT for					
	Group I		Group II		Group III	
	No	SD	No	SD	No	SD
Present	1.55	0.35	1.85	0.25	-	-
Absent	0.72	0.25	1.21	0.5	0.59	0.1
'p'	0.0205 Significant		0.0015 Significant		-	

Mean CIMT was 1.55mm in group I cases with evidence of PVD compared to 0.72 mm in those without PVD. CIMT was 1.85 mm in group II cases with evidence of PVD compared to 1.21 mm in cases without PVD.

The association was statistically significant in group I (p=0.0205) and group II (p=0.0015).

From the table, it is evident that CIMT is significantly associated with the prevalence of PVD in diabetes.

DISCUSSION

Type 2diabetic patients often have diffuse and multiple cardiovascular lesions, despite having less symptoms than nondiabetic subjects. In fact, the onset of CAD may be a severe or fatal event in diabetic patients. The prognosis of cardiovascular events in diabetic patients tends to be worse than that in nondiabetic subjects. Carotid intima media thickness is one of the ways to screen asymptomatic diabetic patients for significant CAD.

In the present study, we investigated the association between carotid atherosclerosis (measured from IMT) and CAD in Indian patients with asymptomatic type 2 diabetes mellitus.

AGE:

The mean age group of patients in the study was 51 yrs and the highest number of patients were in the age group of 40-60 yrs.The age distribution was equal among the three groups with no statistically significant difference (p=0.2135).

Of the 70 patients in this age group, CIMT value was maximum in the CAD group with a mean of 1.3 mm. Further, there was significant correlation of CIMT with advancing age which was statistically significant. This association is in concordance with Studies by J Ahmad et al [48] and Hamma S et al [49] which also showed that CIMT increases with age.

SEX:

There were 61 males and 19 females patients in the study.The mean CIMT was not statistically different between males and females in group I 0.83 vs. 0.66 mm (p=0.3089), group II 1.35 vs. 1.26 mm (p=0.7234) and group III 0.58 vs. 0.62 mm (p=0.6081). None of which was statistically significant. In our study, gender was not found to be an independent risk factor for CIMT.

BMI :

In our study, the mean BMI values were 26.4 in group I, 27.4 in group II and 25.6 in group III respectively. The corresponding mean CIMT values were 0.79 mm in group I, 1.33 mm in group II and 0.59 mm in group III, which showed significant difference between the groups (p=0.0001).

Studies done by Naomi Mitshuashi et al [50] and Kotsis, vasilios t. et al [51] showed similar association. An Indian study done by J Ahmad et al [48] also showed significant correlation between increasing BMI and CIMT.

DURATION OF DM :

In our study, highest value of CIMT was seen in patients who had duration of DM>15 years (1.3mm in group I and 1.7 mm in group II). The mean CIMT values showed increasing values as duration of DM increased, and the association was statistically significant (p=0.0136 in group I and p=0.0003 in group II). This is in concordance with the study done by J Ahmad et al [48] .

On the contrary, in the study conducted by Naomi Mitsuhashi et al [50] , there was no significant association between duration of DM and CIMT (p=0.5054). This could be explained by the fact that this study used diabetics without evidence of CAD as control population, whereas in our study, they were included as cases and non-diabetics were used as controls.

HYPERTENSION :

In our study, hypertension was present in 32.5% of the diabetics(21.7% in group I and 50% in group II). Mean CIMT in hypertensive diabetics was 1.12mm compared to 0.7mm in non-hypertensives in group I (p=0.0237). Mean CIMT was 1.61mm in hypertensive cases in

group II compared to 1.05 mm in non-hypertensive cases in group II (p=0.0032). This shows that hypertension is independently associated with CIMT.

Massimo Puato et al [52] in in his work on CIMT and hypertension, also found that hypertension had a linear correlation with CIMT, which supports the findings of our study.

SMOKING :

In our study, there was statistically significant association between mean CIMT values and smoking in diabetics with CAD group (p=0.01518). This shows a significant relation of CIMT with the prevalence of smoking among diabetics with CAD. CIMT values of smokers in the Non- CAD diabetic group did not show any significance. This could be explained by the fact that cases in the CAD group had more number of risk factors for atherosclerosis compared to the Non-CAD group.

In a study done by Masoume Sadegi et al [53] , there was similar results obtained , correlating CIMT with smoking.

ALCOHOL :

Our study showed that 32.5% of total cases were alcoholic. CIMT in alcoholics belonging to group I was 0.75 mm compared to 0.82 mm in non-alcoholics. The difference was not statisitically significant (p=0.95). CIMT in alcoholics belonging to group II was 1.46 mm compared to 1.25 mm in non- alcoholics in that group. The difference was again not statistically significant (p=0.1936).

Hence, our study shows that CIMT does not correlate with alcohol intake. *Study conducted by Zureik, Mahmoud MD, PhD et al* [54] , comprising of a study population sample of 6216 subjects, showed that CIMT was not associated with alcohol consumption categories in the overall population. Weak and marginal positive

associations were observed between categories of alcohol consumption and carotid plaques in men (P=0.02 for linear trend).

In another study conducted by Ulf Schminke et al [55] , in Germany, as a part of SHIP study, comprising 1230 men and 1190 women, with a cross-sectional design, alcohol use was found to be inversely correlated with carotid IMT as a surrogate marker of generalized atherosclerosis in men but not in women.

Thus, the association of alcohol with CIMT is controversial, with different studies providing conflicting reports. Further studies with more stringent protocols are needed to clarify its role in subclinical atherosclerosis.

FASTING HYPERGLYCEMIA :

Our study showed that mean CIMT significantly associated with fasting hyperglycemia in the CAD group, compared to non-CAD patients, with a 'p' value of 0.0046.

In a similar study conducted by J Ahmad et al [48] , CIMT showed significant correlation with fasting plasma glucose ($r=0.271$, $p<0.05$).

Khamseh ME et al [56] also showed that showed that fasting blood glucose is an important factor that may affect carotid intima-media thickness.

TOTAL CHOLESTEROL :

In our study, CIMT showed a significant association with hypercholesterolemia in diabetics belonging to both CAD (CIMT-1.6 vs. 0.97) and NON-CAD groups(CIMT 1.1 vs 0.59), compared to the controls. There was significant association among the CAD group compared to the non-CAD group ('p' value 0.016).

In the study conducted by Khamseh ME et al [56] , it was proved that Diabetic dyslipidemia significantly affected the carotid intima media thickness.

RETINOPATHY :

Our study shows that in CAD and NON-CAD cases, mean CIMT showed significant association with the prevalence of diabetic retinopathy, with 'p' values of 0.0097 (group I) and 0.0112(group II) respectively, compared to controls.

MOHAN REMA, MBBS, DO, PHD, FABMS and VISWANATHAN MOHAN, MD, MRCP, PHD, DSC,FNASC et al [57] in the the Chennai Urban Rural Epidemiology Study (CURES-2) trial, which comprised of 600 type 2 diabetic subjects randomly selected from Chennai, showed that Mean values of IMT (0.93 _ 0.36 vs. 0.85 _ 0.21 mm, *P* _ 0.001) were significantly higher among diabetic subjects with retinopathy.

NEPHROPATHY :

Our study showed that CIMT was higher in diabetics with nephropathy in group I and group II. The association showed statistical significance in group I (p=0.0205) and group II (p=0.0081).The strength of association was higher in cases with CAD.

The result shows that CIMT was signifaicantly associated with the prevalence of nephropathy in diabetics.

The study by Nathan et al. [58] also illustrates the relation of microalbuminuria to vascular complications such as intima–media thickening.

PERIPHERAL VASCULAR DISEASE :

In our study, the prevalence of PVD among diabetics was 12.5%.

Mean CIMT was 1.55mm in group I cases with evidence of PVD and CIMT was 1.85 mm in group II cases with no evidence of PVD. The association was statistically significant in group I (p=0.0205) and group II (p=0.0015), more so in cases with CAD.

From table 26, it is evident that CIMT bears a significant correlation with PVD in type 2 diabetics.

Ravi R Kasliwal et al [59] showed that There was a significant correlation between brachial-ankle pulse wave velocity and both mean and maximum carotid intima-media thickness in patients with coronary artery disease ($r = 0.47$, $p < 0.0001$ and $r = 0.41$, $p < 0.0008$ respectively) but not in individuals without coronary artery disease ($r = 0.01$ and -0.1) respectively.

Our study is in line with the above study, proving that CIMT has a significant association with PVD in Diabetics with CAD. Hence, PVD could be a strong predictor of CAD in diabetes,along with CIMT.

ASSOCIATION OF CIMT WITH CAD IN TYPE 2 DIABETES :

In our study, there was a 54% prevalence of CAD among asymptomatic type 2 diabetes mellitus patients. Studies conducted by Garcia et al [60] and Bax JJ et al [61] also showed a very high prevalence of CAD among asymptomatic diabetics.

The mean value of CIMT was 0.79 ± 0.35 mm in group I, 1.33 ± 0.52 mm in group II and 0.59 ± 0.1 mm in group III respectively.

There was statistically significant difference in CIMT between the CAD group with Non-CAD group and controls.

There was no significant difference in CIMT value between Non-CAD group and controls.

This agrees with the studies done by Naomi Mitsuhashi et al [50] , J Ahmad et al [48] , Daniel H. O'Leary et al [14] , Folsom AR et al [62] and Yoshimitsu yamasaki, MD, Phd et al [20] . All these studies have shown significant association between CIMT and CAD in type 2 diabetics.

ASSOCIATION OF CIMT WITH ASYMPTOMATIC CAD IN TYPE 2 DIABETES :

Mean CIMT was high in diabetics with Asymptomatic CAD (1.22mm) and MI cases (1.53 mm). The difference was not statistically significant between the groups (p=0.0544). The results thus show that CIMT was associated with CAD in established MI cases as well as in asymptomatic diabetics. When compared to controls, mean CIMT was significantly associated with asymptomatic CAD group (p=0.0001).

Our study is in concordance with the studies conducted by Greenland, P et al [63] , Simon, A et al [64] , Chambless et al [12] , Hodis HN et al [13] and O'Leary et al [14] . Thus our study shows significant association of CIMT in predicting asymptomatic coronary artery disease in type 2 diabetes mellitus patients.

LIMITATIONS OF THE STUDY :

1. The non-CAD patients came from subjects with normal findings on the tread mill testing. However, without coronary angiography, one cannot be completely sure that these subjects were free of CAD. This could be a limitation of our study.

2. Nephropathy was evaluated only based on the urine – macroalbumin positivity, as facilities for detection of microalbuminuria was not available in our hospital. This could lead to underestimation of the prevalence of nephropathy in diabetes and it's association with carotid intima media thickness.

CONCLUSION

- The prevalence of coronary artery disease (TMT positive cases in group II) among asymptomatic type 2 diabetic patients was 54%.
- Mean value of carotid intima media thickness was 1.06±0.4 mm.
- Carotid intima media thickness was significantly associated with coronary artery disease in asymptomatic patients with type 2 diabetes mellitus.
- Age, smoking, body mass index, duration of DM, serum total cholesterol, fasting hyperglycemia, retinopathy, nephropathy and peripheral vascular disease showed correlation with significant carotid intima media thickness in type 2 diabetes mellitus patients.
- Gender and alcoholism were not significantly associated with carotid intima media thickness in type 2 diabetes mellitus patients.
- Our results indicate that early atherosclerosis in the carotid arteries suggests a high probability of coronary involvement in patients with type 2 diabetes mellitus.
- If CIMT is increased in type 2 diabetic patients, further screening for CAD should be performed, and treatment should be initiated to prevent the progression of CAD.

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SUMMARY

Coronary artery disease is a well recognized macrovascular complication in type 2 diabetes mellitus patients.

This study was conducted to find the association between carotid intima media thickness and coronary artery disease among asymptomatic type 2 diabetes mellitus patients.

After institutional ethical clearance, with an informed consent and with rigid inclusion and exclusion criteria, 65 patients and 15 controls were selected carefully and were evaluated on social, clinical and laboratory aspects. The data were entered in Micro soft Excel spread sheet and analyzed statistically.

The Mean age was 51 ±7.5 years. Among 65 type 2 diabetic patients 23 belonged to non-CAD group, 42 belonged to the CAD group. The age groups of all the three groups were comparable and there was no statistical difference (p=0.2135).

There were 61 males and 19 females patients in the study. The mean CIMT was not statistically different between males and females.

There was significant relation of CIMT with the prevalence of smoking among diabetics with CAD.

32.5% of total cases were alcoholic. There was no significant association between the prevalence of alcoholism and mean CIMT.

CIMT was significantly associated with asymptomatic CAD in type 2 diabetes mellitus patients compared to the non-CAD group.

CAD, age, smoking, body mass index, duration of DM, serum total cholesterol, fasting hyperglycemia, retinopathy, nephropathy and peripheral vascular disease were all significantly associated with CIMT in type 2 diabetics.

There is no significant relationship of CIMT with gender and alcoholism.

Further studies comprising of a large number of cases will be needed in the future to determine the exact value of carotid intima media thickness beyond which there will be a significant risk of coronary events in type 2 diabetics.

BIBLIOGRAPHY

1. Chait A, Bierman EL: Pathogenesis of macrovascular disease in diabetes. In *Joslin's Diabetes Mellitus*. Kahn CR, Weir GC, Eds. Philadelphia, Lea and Febiger, 1994, p. 648–664

2. Turner RC, Millns H, Neil HAW, Stratton IM, Manley SE, Matthews DR, Holman RR: Risk factors for coronary artery disease in noninsulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS 23) *BMJ* 316:823–828, 1998

3. Laakso M: Glycemic control and the risk for coronary heart disease in patients with noninsulin- dependent diabetes mellitus: the Finnish studies. *Ann Intern Med* 124:127–130, 1996

4. Pignoli P: Ultrasound B-mode imaging for arterial wall thickness measurement. *Atheroscler Rev* 12:177–184, 1984

5. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R: Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation* 74:1399–1406, 1986

6. Kawamori R, Yamasaki Y, Matsushima H, Nishizawa H, Nao K, Hougaku H, Maeda H, Hanada N, Matsumoto M, Kamada T: Prevalence of carotid atherosclerosis in diabetic patients: ultrasound high-resolution B-mode imaging on carotid arteries. *Diabetes Care* 15:1290–1294, 1992

7. Yamasaki Y, Kawamori R, Matsushima H, Nishizawa H, Kodama M, Kajimoto Y, Morishima T, Kamada T: Atherosclerosis in carotid artery of young IDDM patients monitored by ultrasound high-resolution B-mode imaging. *Diabetes* 43:634–639, 1994

8. Yamasaki Y, Kawamori R, Matsushima H, Nishizawa H, Kodama M, Kubota M, Kajimoto Y, Kamada T: Asymptomatic hyperglycemia is associated with increased intimal plus medial thickness of the carotid artery. *Diabetologia* 38:585–591, 1995

9. Temelkova-Kurktschiev TS, Koehler C, Leonhardt W, Schaper F, Henkel E, Siegert G, Hanefeld M: Increased intimal-medial thickness in newly detected type 2 diabetes: risk factors. *Diabetes Care* 22:333–338, 1999

10. Salonen R, Salonen JT: Progression of carotid atherosclerosis and its determinants: a population-based ultrasonography study. *Atherosclerosis* 81:33–40, 1990

11. Salonen JT, Salonen R: Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. *Arterioscler Thromb* 11:1245–1249, 1991

12. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, Clegg LX: Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993.*Am J Epidemiol* 146:483–494, 1997

13. Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH, Azen SP: The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med* 128:262–269, 1998

14. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr, Cardiovascular Health Study Collaborative Research Group: Carotid artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med* 340:14–22, 1999

15. Reddy KS, Yusuf S. Emerging epidemic of cardiovascular disease in the developing countries. *Circulation* 1998; 97: 596–601

16. Yusuf S. Global burden of cardiovascular disease: a review of the evidence of coronary artery disease in Indians: a global perspective. Sethi KK (ed), 1998

17. Wofford JL, Kahl FR, Howard GR, McKinney WM, Toole JF, Crouse JR 3rd: Relation of extent of extracranial carotid artery atherosclerosis as measured by Bmode ultrasound to the extent of coronary atherosclerosis. *Arterioscler Thromb* 11:1786–1794, 1991

18. Burke GL, Evans GW, Riley WA, Sharrett AR, Howard G, Barnes RW, Rosamond W, Crow RS, Rautaharju PM, Heiss G: Arterial wall thickness is associated with prevalent cardiovascular disease in middle- aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Stroke* 26: 386–391, 1995

19. Laakso M: Hyperglycemia and cardiovascular disease in type 2 diabetes. *Diabetes* 48:937–942, 1999

20. Yamasaki Y, Kodama M, Nishizawa H, Sakamoto K, Matsuhisa M, Kajimoto Y, Kosugi K, Shimizu Y, Kawamori R, Hori M: Carotid intima-media thickness in Japanese type 2 diabetic subjects: predictors of progression and relationship with incident coronary heart disease. *Diabetes Care* 23:1310–1315, 2000

21. Yamamoto M, Egusa G, Yamakido M: Carotid atherosclerosis and serum lipopoprotein(a) concentrations in patients with NIDDM. *Diabetes Care* 20:829–831, 1997

22. Rohani M, Jogestrand T, Ekberg M, Vander Linden J. Kallner G, Jassila R, Agewall. Interelation between the extents of atherosclerosis in the thoraces aorta, carotid intima. Media Atherosclerosis 2005; 179(2): 311-6.

23. Touboul PJ, Hennericim G, Meairs S. Mannheirn intima- media thickness consensus. Cerebrovasc Dis 2004; 18(4): 346-7.

24. Hennerici M, Baezher H, Daffertshfer M. Ultrasound and arterial wall disease. Cerebrovasc Dis 2004; 17: 19-33.

25. Mcneil AM, Rosamound WD, Girman CJ, Heiss G, et al. prevalence of coronary heart disease and carotid arterial thickening in patients with the metabolic syndrome (The ARIC Study). Am J cardio 2004; 94(10): 1249-54.

26. Blankenhorn DH, Selzer RH, Crawford DW, Barth JD, et al .Benefice effects of colestipol niacin therapy on the common carotid artery: two and four-year reduction of intima-media thickness measured by ultrasound. Circulation 1993; 88: 20-28.

27. Deadwania PC, Hunnin ghake DB, Bages HG, Jones PH. Effects of rosurastatin, atrovastatin, simvastatin and privation atherogenic dyslipidemia in patients with Chava cteristics of the metabolic syndrome, Am J Cardiol 2005;
95(3): 360-6.

28. Van Tits, smiled TJ, Vanwissen S, De Graaf J, Stalennoef AF. Effects of atrovstation and Simv-astation on Low- density Lipoprotein subfraction profile, low-density Lipoprotein oxidilability, and antibodies to oxidized low density lipoprotein in reaction to carotid intima thickness in familial hypercholesterolemia. J in vestig med 2004; 53(3): 177-84.

29. Van Wesson S, Smilde TJ, de Groot E, Hutten BA. The significance of Femoral- media thickness and plaque scoring in the Atorvastatin versus simvastatin on Atherosclerosis progression (ASAP) Study. Eur J Cardiovasc Prev Renobil 2003; 10(6): 451-6.

30. Alan S, Ulgen MS, Ozturk O, Alun B, et al. Relation between coronary artery disease, risk factors and intimamedia thickness of carotid, arterial dispensability, and stiffness index. Angiology 2003; 54(2): 261-4.

31. Samson RH, Yungst Z, Showalter DP. Homoc-ysteine, As a risk factor for carotid atherosclerosis, is not a risk factorfor early recurrent carotid stenosis following carotid ardor terectomy. Vasc Endo-vascular surg 2004; 38(4): 345-8.

32. Wagenknecht LE, Langefeld CO, Carr JJ, Riley W, et al. Race-Specific relationships between coro-nary and carotid artery calcification and carotid in tima medial thickness. Stroke 2004; 355): 94-9.

33. Admas MR, Nakajomi A, Keech A, Robinson J, et al. Carotid intima-media thickness is only weakly correlated with the extend and severity of coronary artery. Circulation
1995; 92: 2127-2134.

34.Modified from Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 285:2486, 2001.

35. Morrow D et al: Chronic ischemic heart disease, in *Braunwald's Heart Disease,* 7th ed, D Zipes et al (eds). Philadelphia, Saunders, 2005

36. Lee TH et al: Noninvasive tests in patients with stable coronary artery disease. N Engl J Med 344:1840, 2001 [PMID: 11407346]

37.Gibbons RJ et al: ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for the Management of Patients with Chronic Stable Angina), 2002.

38. Pretre R et al: Choice of revascularization strategy for patients with coronary artery disease. JAMA 285:992, 2001 [PMID: 11209153]

39.Smith SC Jr et al: ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). American College of Cardiology.

40. Harrison's Principle's of Internal Medicine 17th edition

41. Wong M, Edelstein J, Wollman J *et al*. Ultrasonic-pathological comparison of the human arterial wall. Verification of intima-media thickness. *Arterioscler Thromb* 1993;13:482-6.

42.The Association of Carotid Intima-Media Thickness and Postprandial Dyslipidemia in Patients with Type 2 Diabetes Khamseh ME, Soltani K, Rafiee J, Mokhber A, Baradaran H *Int J Endocrinol Metab 2007; 1: 5-8*

43.Triglyceride Levels and its Correlation with Carotid Intima-Media Thickness *Dharmalingam* Mala[1], *Deshpande* Neeta R[2], *Vidyasagar* Sudha[3] International Journal of Diabetes 2004; vol 24

44. Poli A, Tremoli E, Colombo A, Sirtori M, Pignoli P, Paoletti R. Ultrasonographic measurement of the common carotid artery wall thickness in hypercholesterolemic patients: a new model for the quantitation and follow-up of preclinical atherosclerosis in living human subjects. *Atherosclerosis*. 1988;70:253–261.

45. Mannami T, Konishi M, Baba S, Nishi N, Terao A. Prevalence of asymptomatic carotid atherosclerotic lesions detected by high-resolution ultrasonography and its relation to cardiovascular risk factors in the general population of a Japanese city: the Suita study. *Stroke*. 1997;28: 518–525.

46. Bots ML, Breslau PJ, Briet E, de Bruyn AM, von Vliet HH, vanden Ouweland FA, de Jong PT, Hofman H, Grobbee DE. Cardiovascular determinants of carotid artery disease: the Rotterdam Elderly Study. *Hypertension*. 1992;19:717–720.

47. Burke GL, Evans GW, Riley WA, Sharrett AR, Howard G, Barnes RW, Rosamond W, Crow RS, Rautaharju PM, Heiss G. Arterial wall thickness is associated with prevalent cardiovascular disease in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Stroke*. 1995; 26:386 –391.

48. J Ahmad et al. Inflammatory Markers, Insulin Resistance and Carotid Intima-Media Thickness in North-Indian Type 2 Diabetic Subjects. JAPI • VOL. 55 • OCTOBER 2007

49. Hamma S et al , (Stroke 2001 April; 32(4) : 830-5.

50. NAOMI MITSUHASHI, MD et al; Coronary Artery Disease and Carotid Artery Intima-Media Thickness in Japanese Type 2 Diabetic Patients; *Diabetes Care* 25:1308–1312, 2002.

51. *Vasilios T. Kotsis et al;* Impact of Obesity in Intima Media Thickness of Carotid Arteries; OBESITY Vol. 14 No. 10 October 2006.

52. Puato, M., Palatini, P., Zanardo, M., Dorigatti, F., Tirrito, C., Rattazzi, M., Pauletto, P. (2008). Increase in Carotid Intima-Media Thickness in Grade I Hypertensive Subjects: White-Coat Versus Sustained Hypertension. *Hypertension* 51: 1300-1305.

53. Masoume Sadeghi MD, Hamidreza Roohafza MD, Masoud Poormoghadas MD, Aliakbar Tavassoli MD, Ramin Heidari MD ; IS COMMON CAROTID INTIMA MEDIA THICKNESS AN INDEPENDENT PREDICTOR FOR CORONARY ARTERY DISEASE? ; ARYA Journal 2005 (Spring); Volume 1, Issue 1.

54. *Zureik, Mahmoud MD, PhD et al;* Stroke. 35(12):2770-2775, December 2004.

55. Ulf Schminke, et al ; Association Between Alcohol Consumption and Subclinical Carotid Atherosclerosis ; SHIP trial,Germany.

56. Khamseh ME, Soltani K, Rafiee J, Mokhber A, Baradaran H et al ; The Association of Carotid Intima-Media Thickness and Postprandial Dyslipidemia in Patients with Type 2 Diabetes; *Int J Endocrinol Metab 2007; 1: 5-8.*

57. VISWANATHAN MOHAN, MD, MRCP, PHD, DSC,FNASC et al ; Association of Carotid Intima-Media Thickness and Arterial Stiffness With Diabetic Retinopathy The Chennai Urban Rural Epidemiology Study (CURES-2) ; DIABETES CARE, VOLUME 27, NUMBER 8, AUGUST 2004.

58. Nathan et al ; The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Intensive diabetes therapy and carotid intima–media thickness in type 1 diabetes mellitus. N Engl J Med 2003;348:2294-303.)

59. Ravi R Kasliwal et al ; Carotid-Intima-Media-Thickness-and-Brachial-Ankle Pulse Wave Velocity in Patients with and without Coronary Artery Disease ; (Indian Heart J 2004; 56: 117–122).

60. Garcia MJ, McNamara PM, Gordon T, Kannel WB: Morbidity and mortality in diabetics in the Framingham population: sixteen year follow-up study. *Diabetes* 23:105–111, 1974.

61. BAX JJ et al : Screening for coronary artery disease in patients with diabetes. Diabetes care 30:2729 , 2007.

62. Folsom AR et al(. Prediction of coronary heart disease in middle-aged adults with diabetes. Diabetes Care 2003;26:2777–2784).

63. Greenland, P., Lloyd-Jones, D. (2008). Defining a Rational Approach to Screening for Cardiovascular Risk in Asymptomatic Patients. *J Am Coll Cardiol* 52: 330-332.

64. Simon, A., Chironi, G., Levenson, J. (2007). Comparative performance of subclinical atherosclerosis tests in predicting coronary heart disease in asymptomatic individuals. *Eur Heart J* 28: 2967-2971.

65. Blandine Janand-Delenne et al ; Diabetes Care 22(9):1396-1400, 1999. © 1999 American Diabetes Association, Inc

66. Naka M et al ; Silent myocardial ischemia in patients with non-insulin-dependent diabetes mellitus as judged by treadmill exercise testing and coronary angiography ; The American heart journal **ISSN** 0002-8703; 1992, vol. 123.

CASE PROFORMA

Name : Age : Sex : OP/IP No:
Occupation :
Address :
Phone :

Chief Complaints :

HISTORY :
h/o HTN
h/o DM
h/o smoking - duration pack years
h/o alcoholism – duration quantity

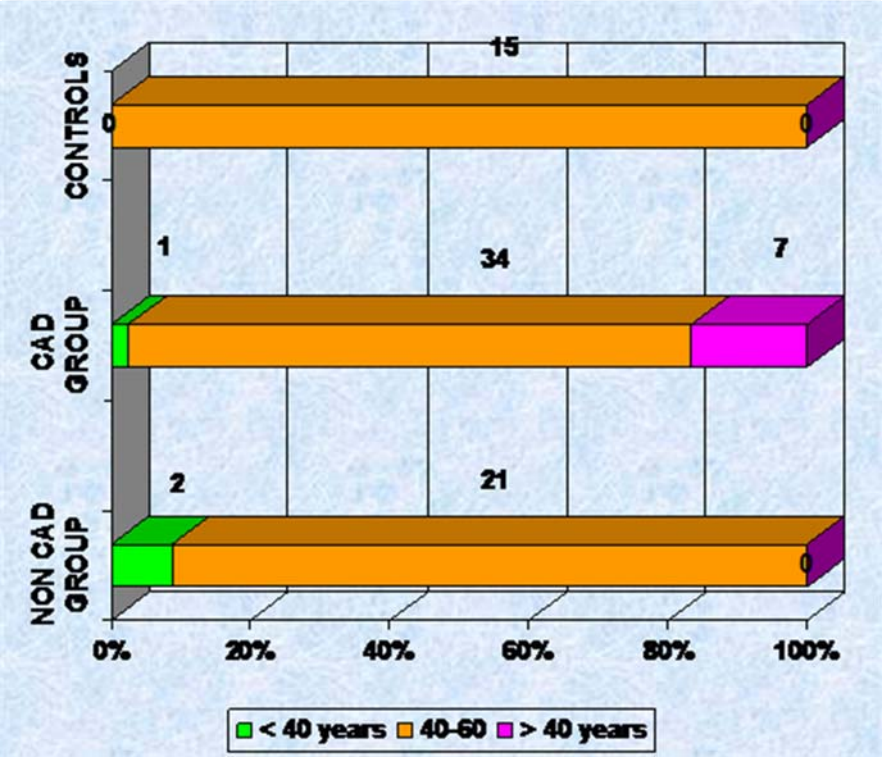
GENERAL EXAMINATION :
Wt. - Ht. - BMI - WHR –
Pallor Icterus Cyanosis Clubbing Pedal edema
JVP Lymphadenopathy Xanthomas Skin tags Acanthosis
VITALS :
Pulse - Rate Rhythm Character Volume
Carotids Femoral
Radial Popliteal
Brachial Post. Tibial
Dorsalis pedis
BP - Rt. UL Lt. UL Rt. LL Lt.LL
RR –

CVS :
RS :
P/A :
CNS : FUNDUS :

INVESTIGATIONS :
Blood Sugar – Fasting Post-prandial
Blood Urea
Serum creatinine
Urine – Albumin Sugar Deposits
Lipid Profile – TC LDL HDL VLDL TG
ECG –
TMT –
CIMT - Rt. Lt. Mean CIMT -

ECHO –

AGE DISTRIBUTION



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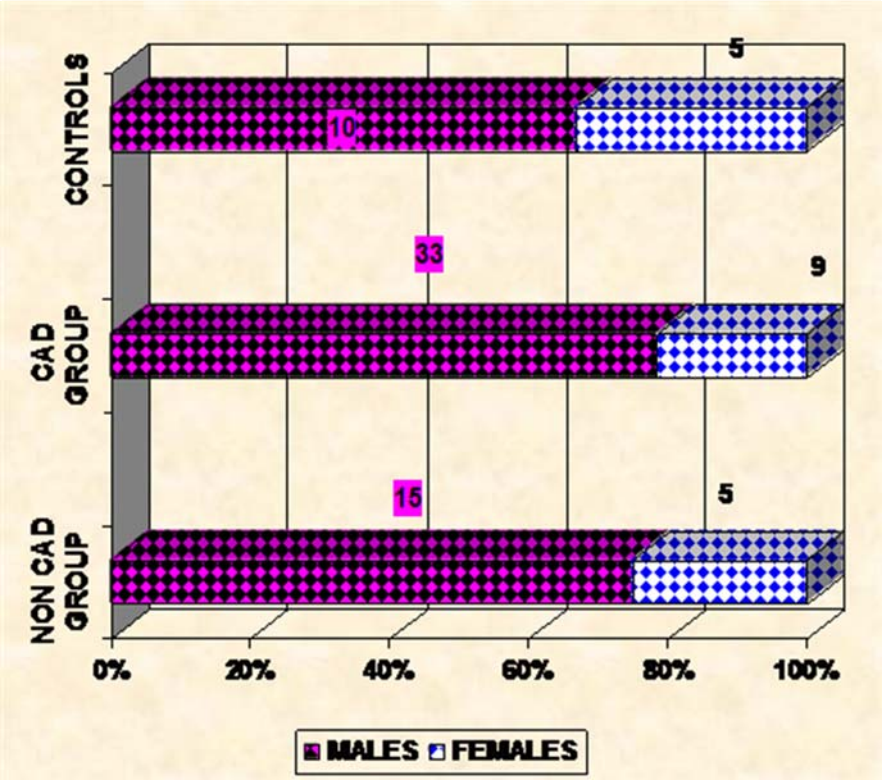
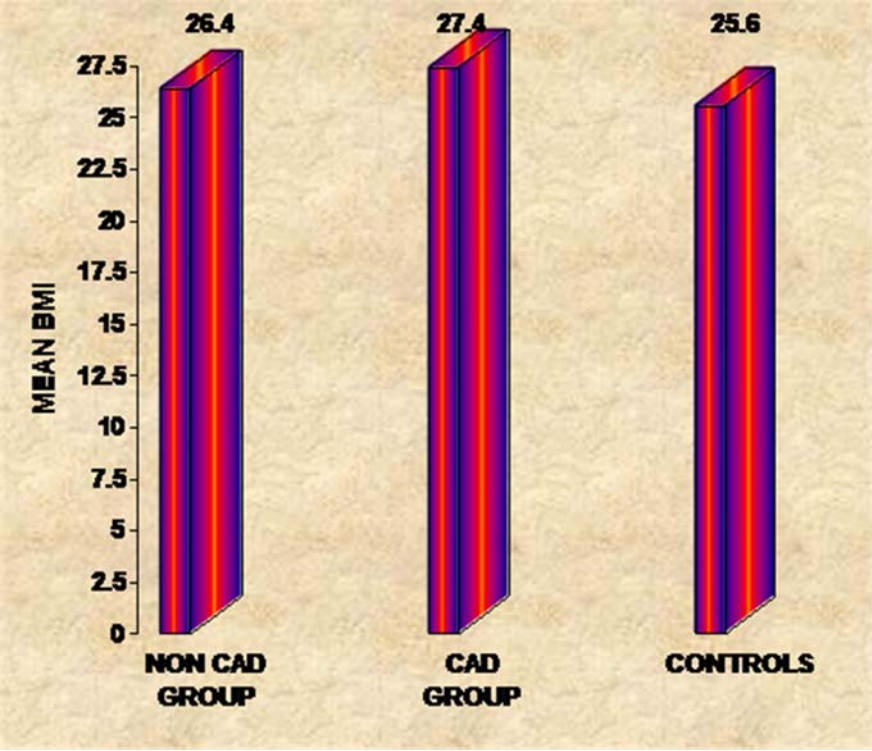
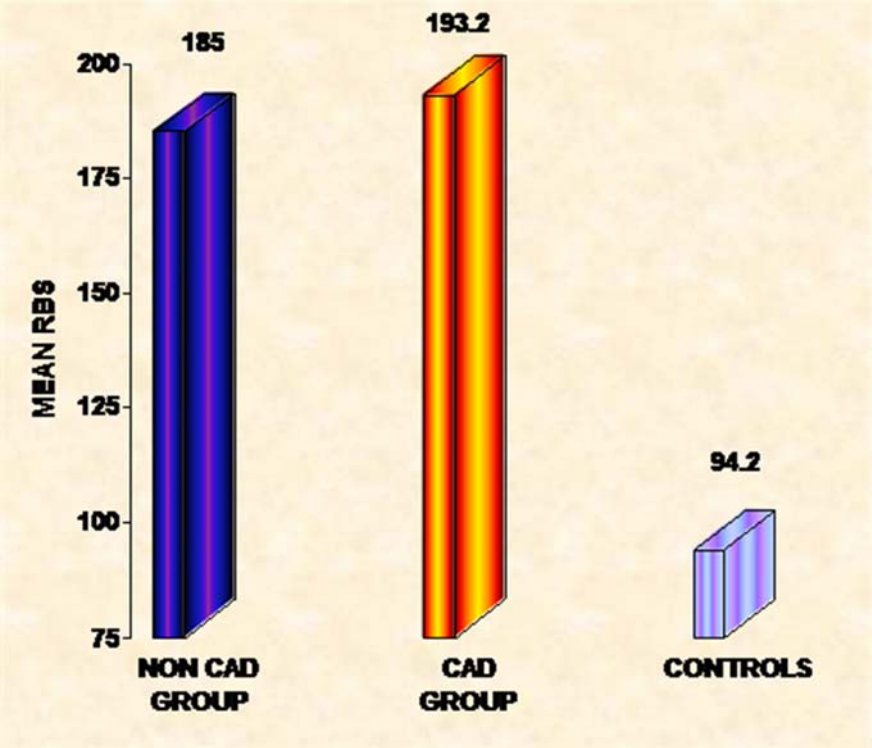


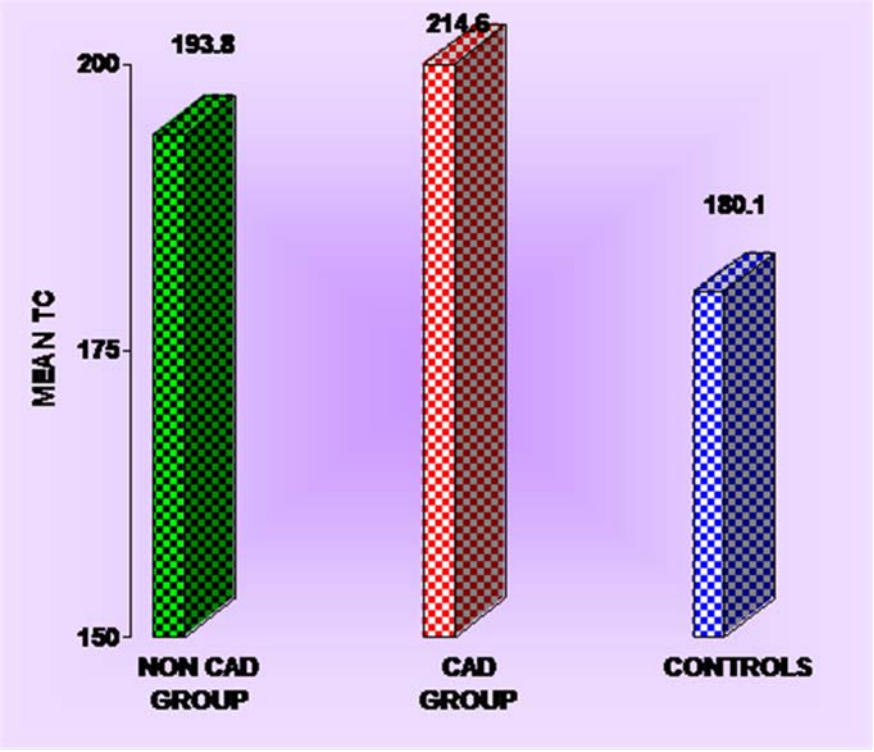
BMI DISTRIBUTION IN THE THREE GROUPS



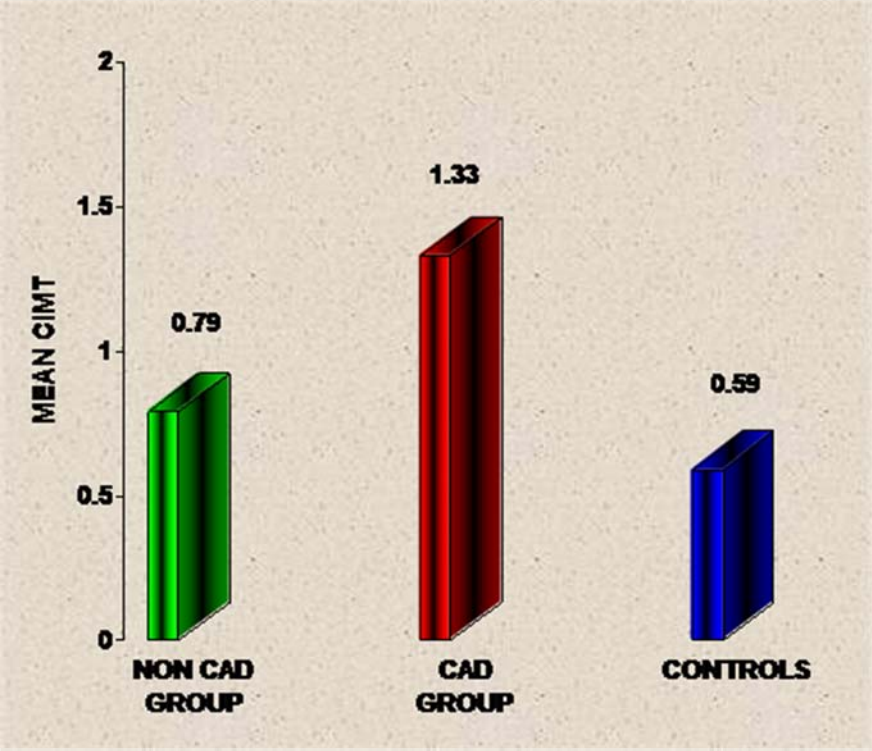
FASTING BLOOD SUGAR – GROUP DISTRIBUTION



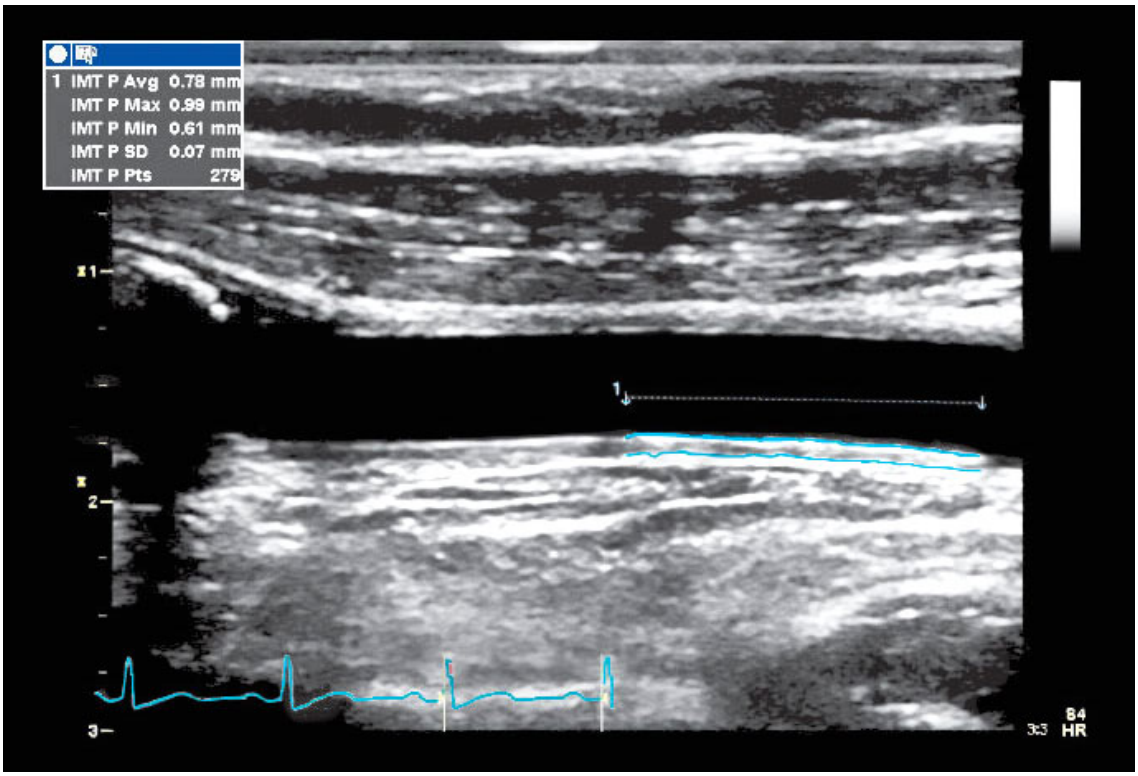
TOTAL CHOLESTEROL – GROUP DISTRIBUTION



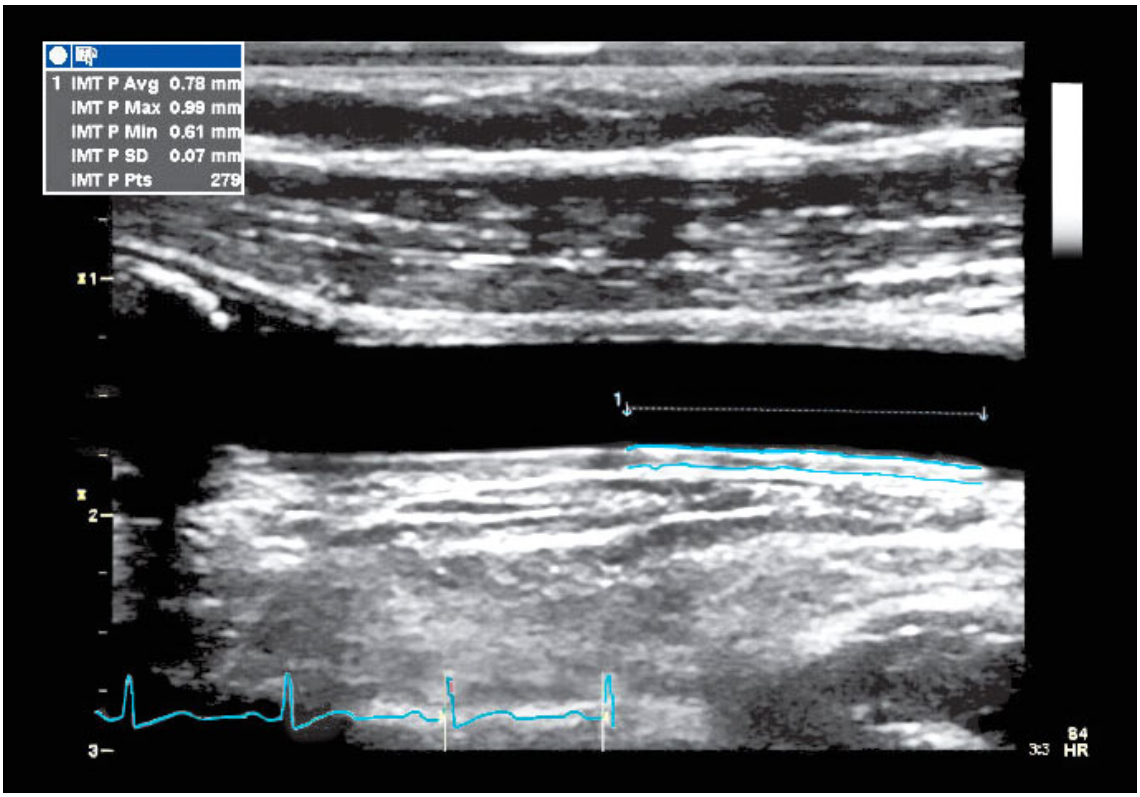
CIMT - GROUP DISTRIBUTION



EVALUATION OF CAROTID INTIMA MEDIA THICKNESS :



EVALUATION OF CAROTID INTIMA MEDIA THICKNESS :



POSITIVE EXERCISE INDUCED ISCHEMIA ON TREADMILL TEST